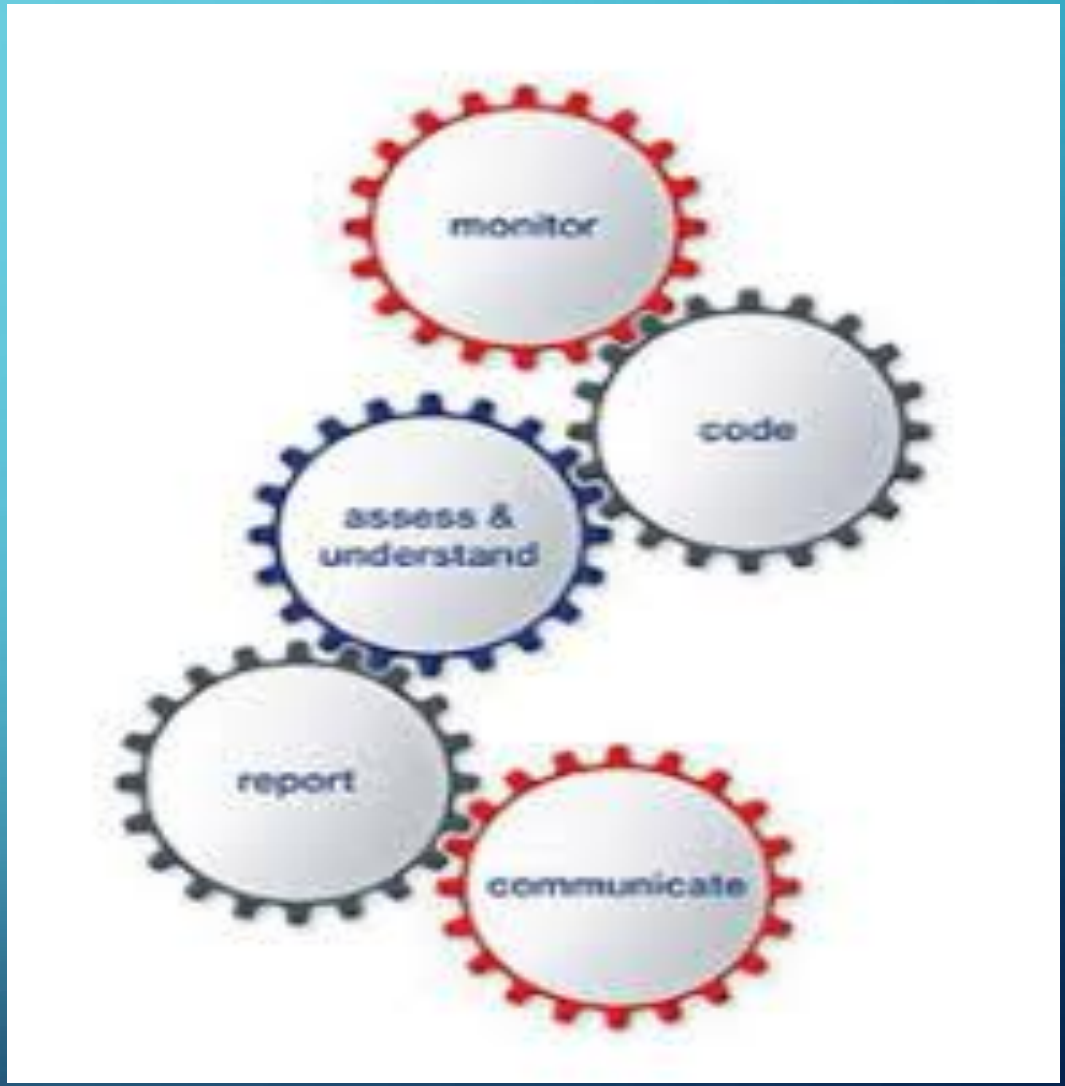
PHARMACOVIGILANCE

What is Pharmacovigilance ?

- Pharmakon (Greek) = Medicinal Substances
- Vigilia (Latin) = To keep watch

WHO Definition

- The science & activities relating to the detection, assessment, understanding & prevention of adverse effects or any other drug related problems



PHARMACOVIGILANCE AUDIT & INSPECTION

PHARMACOVIGILANCE AUDIT

- Pharmacovigilance audit activities should verify, by examination and evaluation of objective evidence, the appropriateness and effectiveness of the implementation and operation of a pharmacovigilance system, including its quality system for pharmacovigilance activities.
- In general, an audit is a systematic, disciplined, independent and documented process for obtaining evidence and evaluating the evidence objectively to determine the extent to which the audit criteria are fulfilled, contributing to the improvement of risk management, control and governance processes.

PV AUDIT /THE RISK-BASED APPROACH TO PV AUDITS

The risk-based approach to audits focuses on the areas of highest risk to the organization's pharmacovigilance system, including its quality system for pharmacovigilance activities. In the context of pharmacovigilance, the risk to public health is of prime importance. Risk can be assessed at the following stages:

- Strategic level audit planning resulting in an audit strategy (long term approach), which should be endorsed by upper management
- Tactical level audit planning resulting in an audit programme, setting audit objectives, and the extent and boundaries, often termed as scope, of the audits in that programme
- Operational level audit planning resulting in an audit plan for individual audit engagements, prioritizing audit tasks based on risk and utilising risk-based sampling and testing approaches, and reporting of audit findings in line with their relative risk level and audit recommendations in line with the suggested grading system

PV AUDIT/ STRATEGIC LEVEL AUDIT PLANNING

The audit strategy is a high level statement of how the audit activities will be delivered over a period of time, longer than the annual programme, usually for a period of 2-5 years.

The audit strategy includes a list of audits that could reasonably be performed. The audit strategy is used to outline the areas highlighted for audit, the audit topics as well as the methods and assumptions (including e.g. risk assessment) on which the audit programme is based.

PV AUDIT/ STRATEGIC LEVEL AUDIT PLANNING

- The audit strategy should cover the governance, risk management and internal controls of all parts of the pharmacovigilance system including:
  - All pharmacovigilance processes and tasks.
  - The quality system for pharmacovigilance activities.
  - Interactions and interfaces with other departments, as appropriate.
  - Pharmacovigilance activities conducted by affiliated organisations or activities delegated to another organisation (e.g. regional reporting centres, MAH affiliates or third parties, such as contract organisations and other vendors).

PV AUDIT/ STRATEGIC LEVEL AUDIT PLANNING

- This is a non-prioritized, non-exhaustive list of examples of risk factors that could be considered for the purposes of a risk assessment:
- 1- Changes to legislation and guidance
- 2- Major re-organization or other re-structuring of the pharmacovigilance system, mergers, acquisitions (specifically for marketing authorization holders, this may lead to a significant increase in the number of products for which the system is used)
- 3- Change in key managerial function
- 4- First medicinal product on the market (for a marketing authorization holder)

PV AUDIT/ STRATEGIC LEVEL AUDIT PLANNING

- 5- Risk to availability of adequately trained and experienced pharmacovigilance staff, e.g. due to significant turn-over of staff, deficiencies in training processes, re-organization, increase in volumes of work
- 6- Significant changes to the system since the time of a previous audit, e.g. introduction of a new database(s) for pharmacovigilance activities or of a significant upgrade to the existing database(s), changes to processes and activities in order to address new or amended regulatory requirements
- 7- Medicinal product(s) on the market with specific risk minimization measures or other specific safety conditions such as requirements for additional monitoring

PV AUDIT/ STRATEGIC LEVEL AUDIT PLANNING

- 8- Criticality of the process, e.g.:
  - For national medicines authorities: how critical is the area/process to proper functioning of the pharmacovigilance system and the overall objective of safeguarding public health;
  - For marketing authorization holders: how critical is the area/process to proper functioning of the pharmacovigilance system. When deciding when to audit an affiliate or third party, the marketing authorization holder should consider the nature and criticality of the pharmacovigilance activities that are being performed by an affiliate or third party on behalf of the marketing authorization holder, in addition to considering the other factors included in this list
- 9- Outcome of previous audits, e.g. has the area/process ever been audited (if not, then this may need to be prioritized depending on criticality); if the area/process has previously been audited, the audit findings* are a factor to consider when deciding when to re-audit the area/process, including the implementation of agreed actions

PV AUDIT/ STRATEGIC LEVEL AUDIT PLANNING

- 10- Identified procedural gaps relating to specific areas/processes.
- 11- Other information relating to compliance* with legislation and guidance, for example:
  - For national medicines authorities: information from compliance* metrics from complaints, from external sources, e.g. audits/assessments of the national medicines authority that may be conducted by external bodies.
  - For marketing authorization holders: information from compliance* metrics from inspections see Module III, from complaints, from other external sources, e.g. audits.
- 12- Other organisational changes that could negatively impact on the area/process, e.g. if a change occurs to a support function (such as information technology support) this could negatively impact upon pharmacovigilance activities.

PV AUDIT/ TACTICAL LEVEL AUDIT PLANNING

- An audit programme is a set of one or more audits planned for a specific timeframe, normally for a year. It should be prepared in line with the long term audit strategy. The audit programme should be approved by upper management with overall responsibility for operational and governance structure.

PV AUDIT/ TACTICAL LEVEL AUDIT PLANNING

- The risk-based audit programme should be based on an appropriate risk assessment and should focus on:
- The quality system for pharmacovigilance activities.
- Critical pharmacovigilance processes.
- Key control systems relied on for pharmacovigilance activities.
- Areas identified as high risk, after controls have been put in place or mitigating action taken.

PV AUDIT/ TACTICAL LEVEL AUDIT PLANNING

- The risk-based audit programme should also take into account historical areas with insufficient past audit coverage, and high risk areas identified by and/or specific requests from management and/or persons responsible for pharmacovigilance activities.
- The audit programme documentation should include a brief description of the plan for each audit to be delivered, including an outline of scope and objectives.
- The rationale for the timing, periodicity and scope of the individual audits which form part of the audit programme should be based on the documented risk assessment.

PV AUDIT/ OPERATIONAL LEVEL AUDIT PLANNING

- *Planning and fieldwork*
- *Reporting*

PV AUDIT/ OPERATIONAL LEVEL AUDIT PLANNING

- *Planning and fieldwork*
- The organization should ensure that *written procedures* are in place regarding the planning and conduct of individual audits that will be delivered. *Timeframes* for all the steps required for the performance of an individual audit should be settled in the relevant audit related procedures, and the organization should ensure that audits are conducted in accordance with the written procedures.
- When planning individual audits, the auditor identifies and assesses the risks relevant to the area under review and employs the most appropriate risk-based sampling and testing methods, documenting the audit approach in an audit plan

PV AUDIT/ OPERATIONAL LEVEL AUDIT PLANNING

- *Reporting*
- The findings of the auditors should be documented in an audit report and should be communicated to management in a timely manner. The audit process should include mechanisms for communicating the audit findings to the auditee and receiving feedback, and reporting the audit findings to management and relevant parties, including those responsible for pharmacovigilance systems, in accordance with legal requirements and guidance on pharmacovigilance audits. Audit findings should be reported in line with their relative risk level and should be graded in order to indicate their relative criticality to risks impacting the pharmacovigilance system, processes and parts of processes.

PV AUDIT/ OPERATIONAL LEVEL AUDIT PLANNING

- The grading system should be defined in the description of the quality system for pharmacovigilance, and should take into consideration the thresholds noted below which would be used in further reporting
- 1- Critical is a fundamental weakness in one or more pharmacovigilance processes or practices that adversely affects the whole pharmacovigilance system and/or the rights, safety or well-being of patients, or that poses a potential risk to public health and/or represents a serious violation of applicable regulatory requirements.

PV AUDIT/ OPERATIONAL LEVEL AUDIT PLANNING

- 2- **Major** is a significant weakness in one or more pharmacovigilance processes or practices, or a fundamental weakness in part of one or more pharmacovigilance processes or practices that is detrimental to the whole process and/or could potentially adversely affect the rights, safety or well-being of patients and/or could potentially pose a risk to public health and/or represents a violation of applicable regulatory requirements which is however not considered serious.
- 3- **Minor** is a weakness in the part of one or more pharmacovigilance processes or practices that is not expected to adversely affect the whole pharmacovigilance system or process and/or the rights, safety or well-being of patients.

ACTIONS BASED ON AUDIT OUTCOMES AND FOLLOW-UP OF AUDITS

- Actions referenced in this section of the guideline, i.e., immediate action, prompt action, action within a reasonable timeframe, issues that need to be urgently addressed, or communicated in an expedited manner, are intended to convey timelines that are appropriate, relevant, and in line with the relative risk to the pharmacovigilance system. *Corrective and preventive actions to address critical and major issues should be prioritised.* The precise timeframe for action(s) related to a given critical finding, for example, may differ depending on nature of findings and the planned action(s).

ACTIONS BASED ON AUDIT OUTCOMES AND FOLLOW-UP OF AUDITS

- The management of the organization is responsible for ensuring that the organization has a mechanism in place to adequately address the issues arising from pharmacovigilance audits. Actions should include root cause analysis and impact analysis of identified audit findings and preparation of a corrective and preventive action plan, where appropriate.

ACTIONS BASED ON AUDIT OUTCOMES AND FOLLOW-UP OF AUDITS

- Upper management and those charged with governance, should ensure that effective action is implemented to address the audit findings. The implementation of agreed actions should be monitored in a systematic way, and the progress of implementation should be communicated on a periodic basis proportionate to the planned actions to upper management.

ACTIONS BASED ON AUDIT OUTCOMES AND FOLLOW-UP OF AUDITS

- Evidence of completion of actions should be recorded in order to document that issues raised during the audit have been addressed.
- Capacity for follow-up audits should be foreseen in the audit programme. They should be carried out as deemed necessary, in order to verify the completion of agreed actions.

QUALITY SYSTEM AND RECORD MANAGEMENT PRACTICES

Independence and objectivity of audit work and auditors

Auditors should be free from interference in determining the scope of auditing, performing pharmacovigilance audits and communicating audit results. The main reporting line should be to the upper management with overall responsibility for operational and governance structure that allows the auditor(s) to fulfil their responsibilities and to provide independent, objective audit opinion.

QUALITY SYSTEM AND RECORD MANAGEMENT PRACTICES

Independence and objectivity of audit work and auditors

Auditors can consult with technical experts, personnel involved in pharmacovigilance processes, and with the person responsible for pharmacovigilance; however auditors should maintain an unbiased attitude that allows them to perform audit work in such a manner that they have an honest belief in their work product and that no significant quality compromises are made. Objectivity requires auditors not to subordinate their judgement on audit matters to that of others.

QUALITY SYSTEM AND RECORD MANAGEMENT PRACTICES

Qualifications, skills and experience of auditors and continuing professional development

The proficiency of audit team members will have been gained through a combination of education, work experience and training and, as a team, should cover knowledge, skills and abilities in:

- Audit principles, procedures and techniques.
- Applicable laws, regulations and other requirements relevant to pharmacovigilance.
- Pharmacovigilance activities, processes and system(s).
- Management system(s).
- Organizational system(s).

AUDITS UNDERTAKEN BY OUTSOURCED AUDIT SERVICE PROVIDERS

- Where the organization decides to use an outsourced audit service provider to implement the pharmacovigilance audit requirements on the basis of this GVP and perform pharmacovigilance audits:
  - The requirements and preparation of the audit risk assessment, the audit strategy and audit programme and individual engagements should be specified to the outsourced service providers, by the organization, in writing.
  - The scope, objectives and procedural requirements for the audit should be specified to the outsourced service provider, by the organization, in writing.
  - The organization should obtain and document assurance of the independence and objectivity of outsourced service providers.
  - The outsourced audit service provider should also follow the relevant parts of this GVP.

Inspection Types

PV-INSPECTION

System and product-related inspections

- Pharmacovigilance system inspections are designed to review the procedures, systems, personnel, and facilities in place and determine their compliance with regulatory pharmacovigilance obligations. As part of this review, product specific examples may be used to demonstrate the operation of the pharmacovigilance system.
- Product-related pharmacovigilance inspections are primarily focused on product-related pharmacovigilance issues, including product-specific activities and documentation, rather than a general system review. Some aspects of the general system may still be examined as part of a product-related inspection (e.g. the system used for that product).

PV-INSPECTION

Routine and “for cause” pharmacovigilance inspections

Routine pharmacovigilance inspections are inspections scheduled in advance as part of inspection programmes. There is no specific trigger to initiate these inspections, although a risk-based approach to optimize supervisory activities should be implemented. These inspections are usually system inspections but one or more specific products may be selected as examples to verify the implementation of the system and to provide practical evidence of its functioning and compliance. Particular concerns, e.g. raised by assessors, may also be included in the scope of a routine inspection, in order to investigate the specific issues.

PV-INSPECTION

Routine and “for cause” pharmacovigilance inspections

For cause pharmacovigilance inspections are undertaken when a trigger is recognized, and an inspection is considered an appropriate way to examine the issues. For cause inspections are more likely to focus on specific pharmacovigilance processes or to include an examination of identified compliance issues and their impact for a specific product. However, full system inspections may also be performed resulting from a trigger.

PV-INSPECTION

Routine and “for cause” pharmacovigilance inspections

For cause inspections may arise when, for example, one or more of the triggers listed below are identified but no limited to:

- 1- Risk-benefit balance of the product
- 2- Reporting obligations
- 3- Requests from the national medicines authorities
- 4- Fulfilment of commitments
- 5- Inspections
- 6- Others

PV-INSPECTION

- For cause inspection cases
- Risk-benefit balance of the product:
  - Change in the risk-benefit balance where further examination through an inspection is considered appropriate.
  - Delays or failure to identify or communicate a risk or a change in the risk-benefit balance.
  - Communication of information on pharmacovigilance concerns to the general public without giving prior or simultaneous notification to the national medicines authorities, as applicable.
  - Non-compliance or product safety issues identified during the monitoring of pharmacovigilance activities by the national medicines authorities;
  - Suspension or product withdrawal with no advance notice to the national medicines authorities

PV-INSPECTION

- **For cause inspection cases**
- Reporting obligations (expedited and periodic):
  - Delays or omissions in reporting
  - Poor quality or incomplete reports
  - Inconsistencies between reports and other information sources

PV-INSPECTION

- <u>For cause inspection cases</u>
- Requests from the national medicines authorities:
  - Failure to provide the requested information or data within the deadline specified by the national medicines authorities;
  - Poor quality or inadequate provision of data to fulfil requests for information from the national medicines authorities

PV-INSPECTION

- **For cause inspection cases**
- Fulfilment of commitments:
  - Concerns about the status or fulfilment of risk management plan (RMP) commitments.
  - Delays or failure to carry out specific obligations relating to the monitoring of product safety, identified at the time of the marketing authorization.
  - Poor quality of reports requested as specific obligations.

PV-INSPECTION

- For cause inspection cases

- Inspections
  - Delays in the implementation or inappropriate implementation of corrective and preventive actions.
  - Information such as non-compliance or product safety issues from other types of inspections (GCP, GMP, GLP and GDP).
  - Inspection information received from other international authorities, which may highlight issues of non-compliance

PV-INSPECTION

- For cause inspection cases

- Others:
  - Concerns following review of the pharmacovigilance system master file.
  - Non-inspection related information received from other authorities, which may highlight issues of non-compliance.
  - Other sources of information or complaints.

PV-REINSPECTION

- A re-inspection may be conducted on a routine basis as part of a routine inspection programme. Risk factors will be assessed in order to prioritize re-inspections. Early re-inspection may take place where significant non-compliance has been identified and where it is necessary to verify actions taken to address findings and to evaluate ongoing compliance with the obligations, including evaluation of changes in the pharmacovigilance system. Early re-inspection may also be appropriate when it is known from a previous inspection that the inspected party had failed to implement appropriately corrective and preventive actions in response to an earlier inspection.

PV– REMOTE INSPECTION

- These are pharmacovigilance inspections performed by inspectors remote from the premises of the marketing authorization holder or firms employed by the marketing authorization holder. Communication mechanisms such as the internet or telephone may be used in the conduct of the inspection. For example, in cases where key sites for pharmacovigilance activities are located outside the Arab Country concerned or a third party service provider is not available at the actual inspection site, but it is feasible to arrange interviews of relevant staff and review of documentation, including the safety database, source documents and pharmacovigilance system master file, via remote access.

PV– REMOTE INSPECTION

- This approach may also be taken where there are logistical challenges to an on-site inspection during exceptional circumstances (e.g. a pandemic outbreak or travel restrictions). Such approaches are taken at the discretion of the inspectors and in agreement with the body commissioning the inspection. The logistical aspects of the remote inspection should be considered following liaison with the marketing authorization holder.
- Where feasible, a remote inspection may lead to a visit to the inspection site if it is considered that the remote inspection has revealed issues which require on-site inspection or if the objectives of the inspection could not be met by remote inspection.

PV INSPECTION PLANNING

- Factors which may be taken into consideration, as appropriate, by the national medicines authorities when establishing pharmacovigilance inspection programmes include, but are not limited to:
- 1- inspection related:
  - compliance history identified during previous pharmacovigilance inspections or other types of inspections (GCP, GMP, GLP and GDP).
  - re-inspection date recommended by the inspectors or assessors as a result of a previous inspection.

PV INSPECTION PLANNING

- Factors which may be taken into consideration, as appropriate, by the national medicines authorities when establishing pharmacovigilance inspection programmes include, but are not limited to:
- 2- product related:
  - product with additional pharmacovigilance activities or risk-minimization activities.
  - authorization with conditions associated with safety, e.g. requirement for post-authorization safety studies (PASS) or designation for additional monitoring.
  - product(s) with large sales volume, i.e. products associated with large patient exposure in the Arab Country concerned.
  - product(s) with limited alternative in the market place.

PV INSPECTION PLANNING

- Factors which may be taken into consideration, as appropriate, by the national medicines authorities when establishing pharmacovigilance inspection programmes include, but are not limited to:
- 3- Marketing authorisation holder related:
  - marketing authorisation holder that has never been subject to a pharmacovigilance inspection.
  - marketing authorisation holder with many products on the market in the Arab Country concerned.
  - resources available to the marketing authorisation holder for the pharmacovigilance activities they undertake.
  - marketing authorisation holder with no previous marketing authorisations in the Arab Country concerned.
  - negative information and/or safety concerns raised by the national medicines authority, other bodies/medicines authorities outside the Arab Country concerned or other areas (i.e. GCP, GMP, GLP and GDP).
  - changes in the marketing authorisation holder organisation, such as mergers and acquisitions

PV INSPECTION PLANNING

- Factors which may be taken into consideration, as appropriate, by the national medicines authorities when establishing pharmacovigilance inspection programmes include, but are not limited to:
- 4- PV system related:
  - QPPV change
  - changes to the pharmacovigilance safety database(s), which could include a change in the database itself or associated databases, the validation status of the database as well as information about transferred or migrated data.
  - changes in contractual arrangements with pharmacovigilance service providers or the sites at which pharmacovigilance is conducted.
  - delegation or transfer of pharmacovigilance system master file management.

PV – ROUTINE INSPECTION

- Individual case safety reports (ICSRs):
- Collecting, receiving and exchanging reports – from all types of sources, sites and departments within the pharmacovigilance system.
- Assessment, including mechanisms for obtaining and recording reporter assessments, company application of event terms, seriousness, expectedness and causality
- Follow-up and outcome recording, for example final outcome of cases of exposure in pregnancy and medical confirmation of consumer reported events;
- Reporting according to the requirements for various types of reported ICSRs, including onward reporting to the relevant bodies and timeliness of such reporting;
- Record keeping and archiving for ICSRs

PV – ROUTINE INSPECTION

- Periodic safety update reports (PBRER), (as applicable):

- Completeness and accuracy of the data included, appropriateness of decisions concerning data that are not included.
- Addressing safety topics, providing relevant analyses and actions.
- Formatting according to requirements.
- Timeliness of submissions.

PV – ROUTINE INSPECTION

- ongoing safety evaluation
- Use of all relevant sources of information for signal detection;
- Appropriately applied methodology concerning analysis.
- Appropriateness of investigations and follow-up actions, e.g. the implementation of recommendations following data review.
- Implementation of the RMP, or other commitments, e.g. conditions of marketing authorization.
- Timely identification and provision of complete and accurate data to the medicines authority of the Arab Country concerned, in particular in response to specific requests for data.
- Implementation of approved changes to safety communications and product information

PV – ROUTINE INSPECTION

- Interventional (where appropriate) and non-interventional clinical trials
- Reporting suspected unexpected serious adverse reactions (SUSARs) and non-interventional study cases according to the national regulations.
- Receiving, recording and assessing cases from interventional and non-interventional trials.
- Submission of study results and relevant safety information (e.g. development safety update reports (DSURs) and information included in PBRERs), where applicable, PASS or post-authorization efficacy studies (PAES) submissions, particularly when associated with specific obligations or RMP commitments.
- Appropriate selection of reference safety information, maintenance of investigator brochures and patient information with respect to safety.
- The inclusion of study data in ongoing safety evaluation

PV – ROUTINE INSPECTION

- Pharmacovigilance system
- QPPV/LSR roles and responsibilities, e.g. access to the quality system, the pharmacovigilance system master file, performance metrics, audit and inspection reports, and their ability to take action to improve compliance;
- the roles and responsibilities of the marketing authorization holder in relation to the pharmacovigilance system;
- accuracy, completeness and maintenance of the pharmacovigilance system master file;
- quality and adequacy of training, qualifications and experience of staff;
- coverage and adherence to the quality system in relation to pharmacovigilance, including quality control and quality assurance processes;
- fitness for purpose of computerized systems;
- contracts and agreements with all relevant parties appropriately reflect responsibilities and activities in the fulfilment of pharmacovigilance, and are adhered to.
- As a general approach, a marketing authorization holder should be inspected on the basis of risk-based considerations, but it is recommended to routinely inspect MAH at least once every 4 years.

Thank
you